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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,538	03/26/2001	Zuomei Li	106101.144	6847

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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	19

DATE MAILED: 08/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,538	LI ET AL.	
	Examiner	Art Unit	
	Mary Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *8-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *16* .

DETAILED ACTION

1. Applicant's election of Group I, SEQ ID NO:2, in Paper No. 18, filed May 10, 2002, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 8-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 18, filed May 10, 2002. Although the elected Group I included claims 1-21 in the restriction (Paper 15, mailed 1/28/02), the subsequent election of SEQ ID NO:2 as the elected gene sequence, includes claims 1-7, but does not further include claims 8-21. Thus claims 8-21 are withdrawn since they do not comprise the elected SEQ ID NO:2.

Furthermore, Applicant is informed now that in the future (corresponding to the issuance of a final rejection), Applicant will be required to cancel the non-elected subject matter, including claims 8-36 and the portions of claims 1-7 not drawn to HDAC-1 (SEQ ID NO:2) and SEQ ID NOS: 17 and 18 which bind HDAC-1.

3. The following Official Action considers on the merits the oligonucleotides of claims 1-7 drawn to inhibition of HDAC-1 (SEQ ID NO:2):

Priority

4. Please note that the claimed subject matter of the instant claim 7 is given priority only to the filing of the instant Application on March 26, 2001, for SEQ ID NOS: 17 and 18. Neither U.S. Provisional Application 60/192,157 nor U.S. Provisional Application 60/261,522, discloses the sequence of instant SEQ ID NOS: 17 and 18. Applicant is requested to clarify by Affidavit or Declaration that the instantly disclosed and claimed SEQ ID NOS: 17 and 18 are the same sequences as MG2608, MG2725, AS1 or MM in the figures of the provisional applications.

Information Disclosure Statement

5. The information disclosure statement filed April 4, 2002, (Paper #16) fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because . 37 CFR 1.98(a)(2) requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The IDS is acceptable except for Reference C10 under "Other Documents", the International Search Report of PCT/US01/09651. Applicant is requested to submit a supplemental IDS having all the specific references cited in the search report as well as copies of those references. Reference C10, the information within the search report, has not been considered on the merits.

Claim Objections

6. Claim 6 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 6 is objected to in view of the election of SEQ ID NO:2 by Applicant in response to the restriction requirement. As such, now claims 1 and 6 are drawn solely to the consideration of SEQ ID NO:2 and thus claim the same subject matter.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 09/817,913. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to have made an oligonucleotide having a nucleotide sequence of from about 13 to about 35 nucleotides that inhibits one or more specific histone deacetylase isoforms, specifically the elected HDAC-1 of instant SEQ ID NO:2, wherein the oligonucleotide is complementary to a region of RNA or double-stranded DNA that encodes a portion of the HDAC-1 since claims 1-3 and claims 6-7 of co-pending Application 09/817,913 claimed agents, specifically oligonucleotides, complementary to a region of RNA or double-stranded DNA encoding a histone deacetylase isoform such as HDAC-1 (also SEQ ID NO:2 in '913), having of from about 13 to about 35 nucleotides. It would have further been *prima facie* obvious for the oligonucleotide (of instant claims 2-4) to have been a chimeric oligonucleotide and/or a hybrid oligonucleotide and/or wherein the oligonucleotide is from about 15 to about 26 nucleotides since claims 4, 5 and 8 of '913 taught those limitations of the oligonucleotides claimed in '913. It would have further been *prima facie* obvious for the oligonucleotides to HDAC-1 (instant claim 5) to have been 20-26 nucleotides in length, having one or more phosphorothioate

internucleoside linkage, and modified so that the terminal four nucleotides at the 5' end of the oligonucleotide and the terminal four nucleotides at the 3' end of the oligonucleotide each have 2'-O-methyl groups attached to their sugar residues as taught in claim 9 of '913. Similarly, it would have been further obvious to target the HDAC-1 gene of instant SEQ ID NO:2 with the sequences of instant SEQ ID NOS: 17 and 18 (instant claims 6 and 7) since claims 10 and 11 of '913 taught the same sequences.

One of ordinary skill it the art would have been motivated to make the oligonucleotides claimed in instant claims 1-7 since the claims 1-11 of '913 embraced making oligonucleotides having the same structural limitations of the instant claims as detailed in the previous paragraph above. One of ordinary skill in the art would have had the same expectation of success to make the instantly claimed oligonucleotides to human HDAC-1 (instant SEQ ID NO:2) as one would have had in making the oligonucleotides to human HDAC-1 (SEQ ID NO:2) in '913 since the instant HDAC-1 target sequence is the same as claimed in '913. Similarly, one of ordinary skill in the art would have had an expectation of success to make instant SEQ ID NOS: 17 and 18 (instant claim 7) since claim 11 of '913 claimed the exact same oligonucleotide sequences.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102 and/or 103

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1 and 6 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over the sequence of N_Geneseq_032802, Accession AAN91262/c, from Johnson et al., WO8901773.

N_Geneseq_032802, Accession AAN91262/c taught a sequence of 34 bases having bases 8 to 20 of instant SEQ ID NO:17. This sequence is within the about 13 to about 35 nucleotides that is complementary to a region of RNA or dsDNA that encodes a portion of HDAC-1 as required by instant claims 1 and 6. Although the prior art does not specifically teach the function of inhibiting the HDAC-1, this function is considered an inherent characteristic of the structure of the nucleic acid taught by N_Geneseq_032802, Accession AAN91262/c.

MPEP 2112.01 teaches that "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)." The MPEP further teaches that ""Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

N_Geneseq_032802, Accession AAN91262/c (from Johnson et al.) thus anticipates the claimed invention.

12. Claims 1, 4 and 6 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over the sequence of Sequence 19 from U.S. Patent 5,789,564 (Seidah et al.).

Sequence 19 from U.S. Patent 5,789,564 taught a sequence of 29 bases having bases 7 and 9- 20 of instant SEQ ID NO:17. This sequence is within the about 13 to about 35 nucleotides, or about 15 to about 26 nucleotides, that is complementary to a region of RNA or dsDNA that encodes a portion of HDAC-1 as required by instant claims 1, 4 and 6 absent evidence to the contrary. Although the prior art does not specifically teach the function of inhibiting the HDAC-1, this function is considered an inherent characteristic of the structure of Sequence 19 from U.S. Patent 5,789,564.

MPEP 2112.01 teaches that "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)." The MPEP further teaches that ""Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Sequence 19 from U.S. Patent 5,789,564 (Seidah et al.) thus anticipates the claimed invention.

13. Claims 1 and 6 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over the sequence of Sequence 22 from U.S. Patent 5,569,586 (Pelletier et al.).

Sequence 22 from U.S. Patent 5,569,586 taught a sequence of 32 bases having bases 7 to 20 of instant SEQ ID NO:18. This sequence is within the about 13 to about 35 nucleotides that is complementary to a region of RNA or dsDNA that encodes a portion of HDAC-1 as required by instant claims 1 and 6. Although the prior art does not specifically teach the function of inhibiting the HDAC-1, this function is considered an inherent characteristic of the structure of the nucleic acid taught by Sequence 22 from U.S. Patent 5,569,586.

MPEP 2112.01 teaches that "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially

identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)." The MPEP further teaches that ""Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Sequence 22 from U.S. Patent 5,569,586 thus anticipates the claimed invention.

14. Claim 7 is rejected under 35 U.S.C. 102(a) as being anticipated by WO 00/71703 (11/30/00), Methylgene Inc. (IDS reference B2 from the IDS filed 4/4/02).

Sequence 1 from WO 00/71703 is 100% identical to instantly claimed SEQ ID NO:17.

Since priority of claim 7 is given only to the filing of the instant specification, 3/26/01, and not to the filing of the provisional applications (see explanation under "priority" above), claim 7 is anticipated by WO 00/71703.

15. Claim 7 is rejected under 35 U.S.C. 102(a) as being anticipated by WO 00/23112 (4/27/00), Methylgene Inc. (IDS reference B3 from the IDS filed 4/4/02).

WO 00/23112 teaches two sequences having 100% identical to instantly claimed SEQ ID Nos:17 and 18. (see GenEMBL Accession AAA55801 corresponding to instant SEQ ID NO:17 and GenEMBL Accession AAA55800 corresponding to instant SEQ ID NO:18)

Since priority of claim 7 is given only to the filing of the instant specification, 3/26/01, and not to the filing of the provisional applications (see explanation under "priority" above), claim 7 is anticipated by WO 00/23112.

16. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al. (IDS reference A3, IDS filed 10/09/01) in view of the collection of Taylor et al. (*DDT* Vol. 4, No. 12, 12/12/99, pages 562-567), Bennett et al. (Chapter 2, pages 13-46, from Methods in Molecular Medicine: Antisense Therapeutics, 1996), Baracchini et al. (U.S. Patent 5,801,154) and Cowsert (U.S. Patent 5,951,455) and the sequence of HDAC01 (instant SEQ ID NO:2 from GenBank Accession No. U50079, Applicants own admission, page 9 of specification).

Yoshida et al. is relied upon to teach motivation to specifically inhibit a histone deacetylase for the study of the role of histone acetylation in controlling the chromatin functions in eukaryotic cells (page 17174). They teach that a long felt need existed in the art for "the use of a more specific and potent inhibitor of histone deacetylase... to carry out further more refined analyses" of the role of histone deacetylase. While they taught use of TSA as "an important tool in the analysis of the role of histone acetylation in the regulation of the chromatin structure, differentiation, and the cell cycle" they did not specifically teach antisense to histone deacetylase as a research tool for gene inhibition.

Taylor et al. are relied upon to teach generation of antisense oligonucleotides as a tool in the "efficient evaluation of the sequence data generated by the Human Genome Project" (abstract). They define antisense oligonucleotides as: "short sequences (7-30 nucleotides) of

nucleic acids that bind to a specific region of a target messenger RNA (mRNA)... and can be designed to inhibit any gene target provided that the sequence is known. The specificity and ease of design of ONS make them attractive candidates as therapeutic agents and as research tools for the elucidation of gene function." They further teach on page 563 the rational for modifications of the antisense oligonucleotide including "the incorporation of alkyl groups at the 2'-O position of ribose" to increase the binding affinity of ONS for their target. They teach that not all of the 2'-O positions should be modified since that prevents Rnase H degradation of the oligonucleotide target complex. They do not specifically teach antisense to HDAC-1.

Bennett et al. are relied upon to teach that "the antisense paradigm offers the opportunity to identify rapidly lead compounds based on knowledge of the biology of a disease process, and a relevant target gene sequence. With this information, the practitioner of antisense drug discovery can rapidly design, synthesize, and test a series of compounds in cell culture and determine if the target gene is specifically inhibited." (Page 13) They provide the overall process for design and use of antisense oligonucleotides based on the knowledge of a target gene sequence, but do not provide specific motivation for design of antisense to HDAC-1.

GenBank Accession No. U50079 taught that the sequence of human HDAC-1 (instant SEQ ID NO:2) was known.

Baracchini et al. and Cowsert et al. are both relied upon to teach design of antisense oligonucleotides to a known gene target and modifications of said antisense for improved function *in vitro*. Specifically, Baracchini et al. teach in cols. 4-10 the motivation to design antisense to a known gene target and methods for modifying said antisense for increased

expression. Cowsert et al. teach in cols. 3-12 and 25-32 teach the motivation to design antisense to a known gene target and methods for modifying said antisense for increased expression. Cowsert specifically teaches design of an antisense having 8 to 30 bases (see claim 1). They teach the claimed modifications (hybrids and chimeras as defined on pages 19-20 of the instant specification) of antisense as follows: modified internucleoside linkage; phosphorothioate linkage; at least one modified sugar moiety; a 2'-O-methoxyethyl sugar moiety; at least one modified nucleobase; a 5-methylcytosine base (Cowsert col. 25-col. 34). They also teach a chimeric oligonucleotide (Cowsert col. 33). They taught by example addition of 2'-O-methyl modifications on the wings (5' and 3' ends) of the disclosed antisense oligonucleotides. They do not specifically teach design of antisense to the HDAC-1 gene as instantly claimed.

It would have been *prima facie* obvious to one of ordinary skill in the art to design an antisense to any gene target specifically as a tool for the investigation of the expressed protein function (Taylor et al.), or for the identification of drug candidates (Bennett et al.). It would have been *prima facie* obvious to one of ordinary skill in the art to design an inhibitor of a histone deacetylase, including the instant HDAC-1, for the reasons taught by Yoshida et al. It would have been *prima facie* obvious for one of ordinary skill in the art to have considered the teachings of Taylor et al., Bennett et al., Cowsert and Baracchini et al. for a design of an antisense oligonucleotide having about 13 to about 35 or about 15 to about 26 nucleotides in length, or having 20-26 nucleotides in length and having 2'-O-methyl modifications, specifically targeting the HDAC-1 gene of instant SEQ ID NO:2, since (1) the sequence of human HDAC-1

was known in the art in Genbank Accession U50079 from which to design the complementary antisense sequences, and (3) these claimed sizes and modifications were all disclosed by Taylor et al., Bennett et al., Cowsert and Baracchini et al. as routinely used in the art for improved antisense stability. It thus would have been obvious to one of ordinary skill in the art at the time that the invention to design of oligonucleotides such as those instantly claimed to bind HDAC-1 as a tool for gene specific inhibition of HDAC-1.

One of ordinary skill in the art would have been motivated to make specific inhibitors to histone deacetylase for the reasons taught by Yoshida et al., analysis of the role of the histone deacetylase in the regulation of chromatin structure, differentiation and the cell cycle. One would have been motivated to use antisense as a tool for inhibition of any gene target such as HDAC-1 for the reasons taught by Taylor et al., Bennett et al., Cowsert and Baracchini et al. above. One of ordinary skill in the art thus would have been motivated to combine the teachings of Yoshiba et al. with the teachings of Taylor et al., Bennett et al., Cowsert and Baracchini et al. for making oligonucleotides to inhibit HDAC-1 as instantly claimed as the mechanism for HDAC-1 gene inhibition.

One of ordinary skill in the art would have had an expectation of success to design antisense sequences to HDAC-1 since Bennett et al., Taylor et al., Cowsert and Baracchini et al. all taught that the design of an antisense requires no more than knowledge of the target gene nucleic acid code sequence from which to design the complementary oligos (optionally complexed with modifications thereof for improved inhibition of the target gene in cells in culture) and the sequence of HDAC-1 was known in the art at the time the invention was made.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Kay Pinkney*, whose telephone number is (703) 305-3553.

M. M. Schmidt
July 29, 2002.